PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
10710		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 03638	20/04/2000	23/04/1999
Applicant		
GESELLSCHAFT FUER BIOTECHNOLOGISCHE FORSCHUNG...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03638

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/85 C12N15/63 C12N15/62 C12N5/10 //C07K14/47, C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CAB Data, STRAND, BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 11241 A (VON HOEGEN ILKA ;BRUEMMER WOLFGANG (DE); MERCK PATENT GMBH (DE); B) 19 March 1998 (1998-03-19) page 24, line 13 - line 19; figures 1A,1B	1-4
Y	S. KIRCHHOFF ET AL.: "Regulation of cell growth by IRF-1 in BHK-21 cells" CYTOTECHNOLOGY, vol. 22, 1996, pages 147-156, XP000852635 KLUWER ACADEMIC PUBLISHERS, PRINTED IN THE NETHERLANDS cited in the application the whole document	1-4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2000	11/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornig, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOESTER, MARIO ET AL: "Proliferation control of mammalian cells by the tumor suppressor IRF-1." CYTOTECHNOLOGY, (1995) VOL. 18, NO. 1-2, PP. 67-75., XP002121739 cited in the application the whole document	1-4
Y	KIRCHHOFF, S. ET AL: "Interferon regulatory factor-1 (IRF-1) mediates cell growth inhibition by transactivation of downstream target genes." NUCLEIC ACIDS RESEARCH, (1993 JUN 25) 21 (12) 2881-9. JOURNAL CODE: 08L., XP002121655 cited in the application the whole document	1-4
A	W. DIRKS ET AL.: "A new hybrid promoter directs transcription at identical start points in mammalian cells and in vitro" GENE, vol. 149, 1994, pages 389-390, XP002145693 ELSEVIER SCIENCE PUBLISHERS,B.V.,AMSTERDAM,NL; the whole document	
A	ARTELT P ET AL: "VECTORS FOR EFFICIENT EXPRESSION IN MAMMALIAN FIBROBLASTOID, MYELOID AND LYMPHOID CELLS VIA TRANSFECTION OR INFECTION" GENE,NL,ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 68, no. 2 + INDEX, 1988, pages 213-219, XP000000152 ISSN: 0378-1119 the whole document	
A	FUSSENEGGER ET AL: "Regulated multicistronic expression technology for mammalian metabolic engeneering" CYTOTECHNOLOGY,NL,KLUWER ACADEMIC PUBLISHERS, DORDRECHT, vol. 28, no. 28, 1998, pages 111-125, XP002110264 ISSN: 0920-9069 the whole document	

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1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KIRCHHOFF S ET AL: "NFkappaB activation is required for interferon regulator factor-1-mediated interferon beta induction." EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 APR) 261 (2) 546-54. JOURNAL CODE: EMZ., XP002121741 the whole document	
A	DIRKS W ET AL: "Isolation and functional characterization of the murine interferon-beta 1 promoter." JOURNAL OF INTERFERON RESEARCH, (1989 FEB) 9 (1) 125-33. JOURNAL CODE: IJI., XP002121742 the whole document	
A	FUSSENEGGER M ET AL: "Genetic optimization of recombinant glycoprotein production by mammalian cells" TRENDS IN BIOTECHNOLOGY, vol. 17, no. 1, January 1999 (1999-01), page 35-42 XP004155532 ISSN: 0167-7799 cited in the application the whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/03638

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811241 A	19-03-1998	AU 4208897 A	02-04-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 4

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
10710 -GBF		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03638	20/04/2000	23/04/1999
International Patent Classification (IPC) or national classification and IPC C12N15/85		
Applicant GESELLSCHAFT FUER BIOTECHNOLOGISCHE FORSCHUNG...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/11/2000	30.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Grosskopf, R Telephone No. +49 89 2399 8714

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03638

I. Basis of the r port

1. With regard to the l ments of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-21 as originally filed

Claims, No.:

1-4 as originally filed

Sequence listing part of the description, pages:

1, filed with the letter of 19.07.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Ad it m V:

The quoted documents are:

(1) WO 98 11241 A (VON HOEGEN ILKA ;BRUEMMER WOLFGANG (DE); MERCK PATENT GMBH (DE); B) 19 March 1998 (1998-03-19)
(2) S. KIRCHHOFF ET AL.: "Regulation of cell growth by IRF-1 in BHK-21 cells" CYTOTECHNOLOGY, vol. 22, 1996, pages 147-156

The assembly of two or more known (control) elements in a vector or in a "system" wherein each of said elements merely carries out the function which it is expected to do must, in general, be considered as being non-inventive (e.g. a known promoter with a known gene or a known enhancer with a known promoter). This seems to apply in the present case wherein two known constructs have been assembled in such a system (see e.g. the vectors pMC-1 of D1 with the transactivator control system of e.g. D2).
An inventive activity, therefore, could only be acknowledged if said assembly results in an unexpected or surprising effect. Such an effect, at present, is not recognisable.
Applicant argued that in comparison with D1, the use of the system of the present application results in a 12-fold increase of expression.
In view of D2 this effect, however, cannot be regarded as being surprising.
In fact, D2 both emphasises the general applicability of the inducer element in combination with any promoter (see page 151, right column, last paragraph) and the degree of stimulation which is about ten-fold (see page 154, right column, second paragraph).
Since this degree of stimulation is in the same range as observed in the comparative results presented by the Applicant, said results cannot form the basis for demonstrating the necessary surprising (e.g. synergistic) effect which has to be requested if merely two known elements are combined.

Ad item VIII:

Even if the Applicant will base his arguments on a "selection" with regard to the assembly of the specific elements, this would no longer apply with regard to the

"isofunctional" variants. In fact, said expression, even if interpreted in the light of the description, extends the scope of the various elements to any other "equivalent" element i.e. to any promoter, or any enhancer etc. (or what else should be meant by "the same function"?).

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/85, 15/63, 15/62, 5/10 // C07K 14/47, 14/705

A1

(11) International Publication Number: WO 00/65074

(43) International Publication Date: 2 November 2000 (02.11.00)

(21) International Application Number: PCT/EP00/03638

(22) International Filing Date: 20 April 2000 (20.04.00)

(30) Priority Data:
99108068.0 23 April 1999 (23.04.99) EP

(71) Applicant *(for all designated States except US)*: GESELLSCHAFT FUER BIOTECHNOLOGISCHE FORSCHUNG MBH (GBF) [DE/DE]; Mascheroder Weg 1, D–38124 Braunschweig (DE).

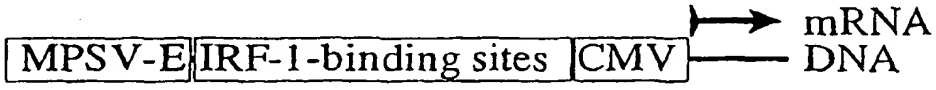
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MUELLER, Peter [DE/DE]; Mascheroder Weg 1, D–38124 Braunschweig (DE). GESERICK, Christoph [DE/DE]; Mascheroder Weg 1, D–38124 Braunschweig (DE). SCHROEDER, Katharina [DE/DE]; Mascheroder Weg 1, D–38124 Braunschweig (DE). HAUSER, Hansjoerg [DE/DE]; Mascheroder Weg 1, D–38124 Braunschweig (DE).

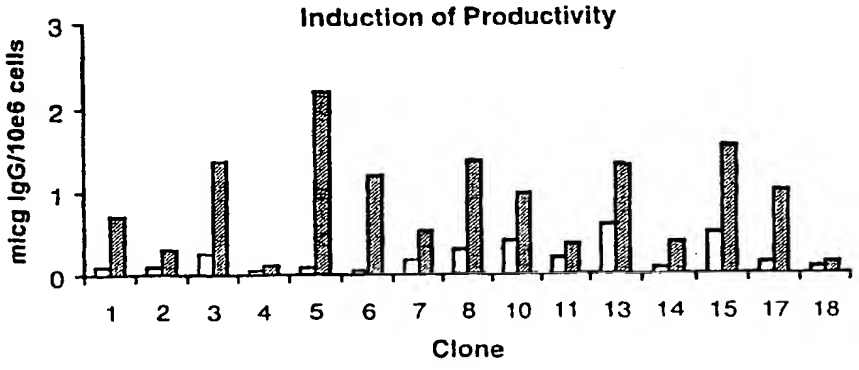
(74) Agents: BOETERS, Hans et al.; Boeters & Bauer, Bereiteranger 15, D–81541 München (DE).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROMOTER–TRANSACTIVATOR SYSTEM FOR INDUCIBLE HIGH–LEVEL MAMMALIAN GENE EXPRESSION WITH THE OPTION OF CELL GROWTH CONTROL





(57) Abstract

A promoter–transactivator system achieves regulated high–level gene expression in proliferation–controlled mammalian cells. The novel composite promoter contains constitutive enhancer elements that allows a basal expression level as high as the levels achieved with a very efficient viral promoter. In addition, the promoter encodes sequences that are bound by a transactivator whose activity can be regulated. By the simple addition of medium supplements expression levels can be achieved above those from the conventional promoter.